

AMENDMENT

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REMARKS

Claims 31-36 are pending. Claims 31 and 36 have been amended.

Claim 31 has been amended to recite that the synthetic hydroxylated triple helical protein "includes one or more non-collagenous, non-triple helical forming domains". Support for this amendment can be found, *inter alia*, at page 7, lines 12-13 of the application as originally filed, which states that:

Synthetic collagen and fragments encompassed by the term "triple helical protein" may also include non-collagenous, non-triple helical domains...

Thus, it is therefore directly and unambiguously derivable support from the application as originally filed that the triple helical proteins of Claim 31 can include more than one non-collagenous, non-triple helical forming domains.

Furthermore, page 7, lines 14-30 of the application as originally filed provides a general formula of the product-encoding nucleotide sequences defined in amended Claim 31, wherein B and C represent non-triple helical forming sequences, and wherein m and o, which define the number of non-triple helical forming sequences present, "are each independently selected from 0 and 1". Therefore, it is immediately apparent from this description of the invention that the product-encoding nucleotide sequence can contain one non-triple helical forming domains. Thus, Applicants respectfully submit that there is a direct and unambiguous support in the application as originally filed for the amendment of Claim 31 to recite that the synthetic hydroxylated triple

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helical protein "includes one or more non-collagenous, non-triple helical forming domains".

On page 2 of the Office Action, the Examiner maintains the rejection of Claims 31-36 under 35 U.S.C. § 102(e) as being anticipated by St. Pierre et al.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Applicants reiterate the submissions previously made and further submit that St. Pierre et al fails to teach or suggest a synthetic recombinant triple helical protein as defined in the amended claims. St. Pierre et al describes collagen mimics of Formula A. These collagen mimics comprises 3 peptide chains linked together by a "Template". This is in contrast to the triple helical proteins of the presently claimed invention, which are formed from collagens according to the formula shown in present Claim 31. The triple helical proteins of the present claims do not require the presence of a template bonding three proteins together to provide stability to the triple helical protein, as is required by the collagen mimic disclosed in St. Pierre et al.

More specifically, St. Pierre et al is concerned with artificial collagen comprising a stabilized ordered triple helix of copolypeptide strands containing repeating amino acid triads of the formula $(X_{aa}-X_{bb}-Gly)-(X_{aa}-X_{bb}-Gly)_n-(X_{aa}-X_{bb}-Gly)-$. The collagen may be modified with groups which improve its physical and chemical properties for the intended use, such as adhesive and cross-linking groups.

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At column 3, lines 29 et seq., St. Pierre et al indicates that the invention described therein, like native collagen, is biocompatible:

...but are of a simplified oligopeptide structure which can be easily synthesised in a laboratory or commercial quantities; the compounds herein also referred to as "collagen mimics", can also be genetically engineered as fusion proteins/polypeptides employing techniques well-known in the art... (emphasis added)

Applicants submit that it is clear from the quoted passage that the reference to "genetically engineered as fusion proteins/polypeptides" is to the "collagen mimics". The "collagen mimics" are described at column 3, lines 61-67, as being characterized by a core comprising an ordered triple helix of at least three copolypeptide strands of repeating amino acid triads ($X_{aa}-X_{bb}-Gly$), each strand being linked at the C-terminal end thereof to a common template for stabilization of the helical secondary structure.

At column 4, lines 13-18, St. Pierre et al states:

The core may also be modified by a polymer for altering the biophysical or biochemical properties of the mimic, covalently linked to the distal end of one or more of the peptide strands or adhesive moiety (AM), or to functional groups on the strand or adhesive moiety backbones, or to the template.

Applicants submit that it is clear from the above statement in St. Pierre et al that the "polymer" is additional to the core, but does not form part of the core (i.e., the collagen mimic).

At column 5, line 41-64, St. Pierre et al states:

In so-modified collagen mimics of the invention, a polymer is included to increase the molecular weight

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of the mimic, and/or to vary other properties of the mimic such as hydrophilicity, immunogenicity, and *in vivo* stability. As indicated in Formula A by "•", the polymer may be activated at one end thereof and grafted to the distal end of one or more of the peptide strands; to the distal end of the adhesive moiety; to the backbones of the strands or adhesive moiety; to the spacer; or to the template, by covalent linkage of the activated groups to appropriate functional side chains or terminal groups of the mimic, especially amino or hydroxy groups. The polymer may also be activated at both ends for cross-linking of the mimic, particularly cross-linking of the peptide strands. Generally, the molecular weight of the polymer is from about 200 to 100,000 daltons, preferably at least about 1,000 daltons. Polyethylene glycol, especially monomethoxypolyethylene glycol, is a particularly suitable polymer for clinical use because of its known efficacies and safety as a protein modifier (*supra*). Polyvinyl alcohol, polyglutamic acid, polyaspartic acid, polylysine, or PluronicTM polymers are also exemplary. The polymer may also be selected for its biodegradability, biocompatibility, benign reactivity with the mimic, and other properties as desired.

It is clear from this passage that St Pierre et al teaches that the "polymer", if used to modify the collagen mimics of the invention, is to be activated and grafted onto, *inter alia*, the peptide strands. However, there is no teaching or suggestion in this passage of recombinantly producing both the collagen mimic and the polymer.

The Examiner previously asserted that St. Pierre et al "... teaches that this polymer can be a peptide selected from polyglutamic acid, polyaspartic acid and polylysine, which meets the claim limitation of at least one peptide domain which is heterologous to collagen proteins which do not comprise a triple helical forming repeating sequence".

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However, the passage cited above indicates that polyethylene glycol, especially monomethoxypolyethylene glycol, is a particularly suitable polymer for clinical use. Indeed, the use of polyethylene glycol is described in detail at column 3, lines 3-17 in St. Pierre et al to the related art. It also cites as suitable polymers, polyvinyl alcohol and "Plurronics™ polymers" (polymers based on ethyleneoxide and propylene oxide - see attached BASF product information).

Furthermore, all three Examples provided in St Pierre et al involve the use of a polymer or copolymer of polyethylene glycol as the polymer. All three Examples are prepared by chemical reaction, including the triads.

Polyethylene glycol, polyvinyl alcohol and "Plurronics™ polymers" cannot be produced recombinantly.

The Examiner also previously referred to the passage at column 6, lines 24-34 which indicates that the oligopolypeptide strands that are comprised of the triple helical forming repeating sequence can be prepared as fusion proteins or peptide fragments thereof from appropriate genetically-engineered expression vectors in suitable host cells. However, that passage, is concerned with "the oligopeptide", which would not be considered by the skilled artisan to include the "polymer" which has been added by modification. Rather it would be understood by the skilled person to be a reference to the core oligopeptide structure (see column 3, lines 37-40), that is, the collagen mimics.

Thus, St. Pierre et al, at most, suggests the possibility of recombinantly producing the "collagen mimics" characterized by a core comprising an ordered triple helix of at least three

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copolypeptide strands of repeating amino acid triads (X_{aa}-X_{bb}-Gly). There is absolutely no teaching or suggestion of producing anything other than the core by recombinant techniques.

In any event, insofar as St. Pierre et al suggest recombinant production of the core, it provides no details on how to produce the core recombinantly. In particular, St. Pierre et al is completely silent on the need to ensure that any recombinant technique is such that there is hydroxylation and Applicants respectfully disagree with the Examiners contention that this would be inherent.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested by St. Pierre et al, and thus request withdrawal of the Examiner's rejection.

On page 6 of the Office Action, the Examiner rejects Claim 36 under 35 U.S.C. § 112, second paragraph.

Specifically, the Examiner states that the expression "exogenous" is a relative term, and without some specific reference to the organism to which the domain is exogenous, the meets and bounds of the claim can not be determined.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

"Exogenous" in Claim 36 finds support at paragraph [0004] of the original specification which states:

... Further, the use of recombinant DNA technology is desirable in that it allows for the potential production of synthetic collagens and collagen fragments which may include, for example, exogenous biologically active domains (i.e. to provide additional protein function) and other useful

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characteristics (e.g. improved biocompatibility and stability).

The skilled person would understand "exogenous" (heterologous) to mean exogenous to collagen protein.

Nonetheless, in view of the amendments to Claim 36, this rejection has been rendered moot.

In view of the amendments to the claims, and the arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at the below listed number on any questions which might arise.

Respectfully submitted,



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